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The autoimmune tautology revisited

1. Introduction

Autoimmune diseases (ADs) have a common pathophysiological mechanism as a consequence of sharing genetic and environmental factors, as well as similar clinical manifestations and therapeutic approaches, which led to the coining of the term autoimmune tautology in 2010 [1]. The arguments supporting this theory (Fig. 1) have been confirmed by several works since then.

Tautology (from Greek *tauto*, "the same" and *logos*, "word/idea") is an obvious statement. In logic, tautology is a formula, which is true in every possible interpretation. Thus, autoimmune tautology means that one AD is similar to a second one, to a third one, and so on. They cannot be equal because the target cell and organ are different in each case, and influencing factors although similar may vary from one patient to another as well as from one population to another.

Since the last summary of evidence about the topic [2] several publications sustaining the theory have been published [1–75] including this special issue [3–10], which are all discussed here.

2. Female preponderance

It is estimated that around 5%-10% of the world population lives with AD, both men and women are affected but around 70–80% are women [11]. The female immune response is stronger than in men, which is believed generates a greater risk of developing ADs, due to female sex hormones, X chromosome genes, and the microbiome, among others [11]. Although female sex hormones play an important role, female predominance has been described in both prepubertal and postmenopausal women, suggesting that there are other associated mechanisms [11]. When there are supernumerary X chromosomes, such as in men with Klinefelter syndrome (47,XXY), the susceptibility for developing systemic lupus erythematosus (SLE) and other ADs is significantly higher than in healthy men. A similar scenario occurs in women with normal karyotype and women with triple X syndrome (47, XXX) who have 25 times more risk of developing SLE [11]. Women with Turner Syndrome (45X0) have a lower risk [11,12].

The X chromosome inactivation (XCI) process occurs in the embryological development [13]. The X-inactive-specific transcript (*XIST*) gene induces epigenetic mechanisms resulting in a change of euchromatin into heterochromatin, which is known to be the inactive form of the genetic material. Consequently, it acts as a "gene silencing" [13]. Despite the inactivation of the X chromosome, about 15% of the genes escape from XCI, resulting in the dual expression ratio of the given gene in females [13]. Many escaped genes do not have a functional homologous gene on the Y chromosome, giving them a specific characteristic [13]. Within the escaped genes are *CD40L*, *CD99*, *LAMP2*, *IRAK1*, *TLR7*, *USP27X*, *DDX3X*, *CXORF21* and *XIAP*, most of them are involved into the innate and adaptive immune system, and their proteins are produced twice in women than in men, due to the expression of two X chromosomes, contributing to the greater susceptibility of ADs in women [13].

Regarding the hormonal imbalance, progesterone, which has high levels in pregnancy as well as in the menstrual cycle at the luteal phase, generates immunosuppression, decreasing inflammatory mediators and inhibiting cellular immune responses such as decreased dendritic cell activation, natural-killer cells (NK), macrophages, and inhibition of the nuclear factor kappa B (NK-kB) [12]. For this reason, progesterone has been associated with a better clinical course of Th-1-mediated diseases such as multiple sclerosis (MS) and rheumatoid arthritis (RA) during pregnancy [12].

Estrogens are also elevated during pregnancy and decreased at menopause. There are shock receptors such as the pulsed estrogen receptor alfa (ERα) on T cells and the estrogen receptor beta (ERβ) on B cells, through which the upregulation of interferon (IFN) regulatory factor 5 (IRF5) and IFN-γ occurs, and at high concentrations they promote the Th2 response [12,14]. On the other hand, androgens induce downregulation of the immune response. In males they promote the *AIRE* gene in the thymus after binding to the androgen receptor, causing an important decrease of the inflammatory response [12].

3. Shared subphenotypes

Multiple subphenotypes are common among systemic ADs, like the age groups predominantly affected, arthralgia, arthritis, photosensitivity, Raynaud's phenomenon, and cardiovascular involvement [2]. The common presence of non-specific antibodies, including antinuclear antibodies (ANA), rheumatoid factor, anti-Ro antibodies [2] all of which disclose a low specificity and are common among several autoimmune conditions. Particular patters of cytokines such as TNF, IL-1, IL-6, IL-10 and IL-17 have also been described in diverse ADs as part of similarities shared by these conditions [2].

4. Polyautoimmunity

Overt polyautoimmunity (PolyA), defined as the presence of two or more well defined ADs in the same patient (Fig. 2), is present in approximately 40% of patients with SLE, Sjögren's syndrome (SS), autoimmune thyroid disease (AITD) and in 20% of RA [2]. Among the risk factors described for developing PolyA, ancestry, gender, education, familial autoimmunity (i.e., coaggregation of ADs) and economic status have been described. Latent polyautoimmunity is more frequent that

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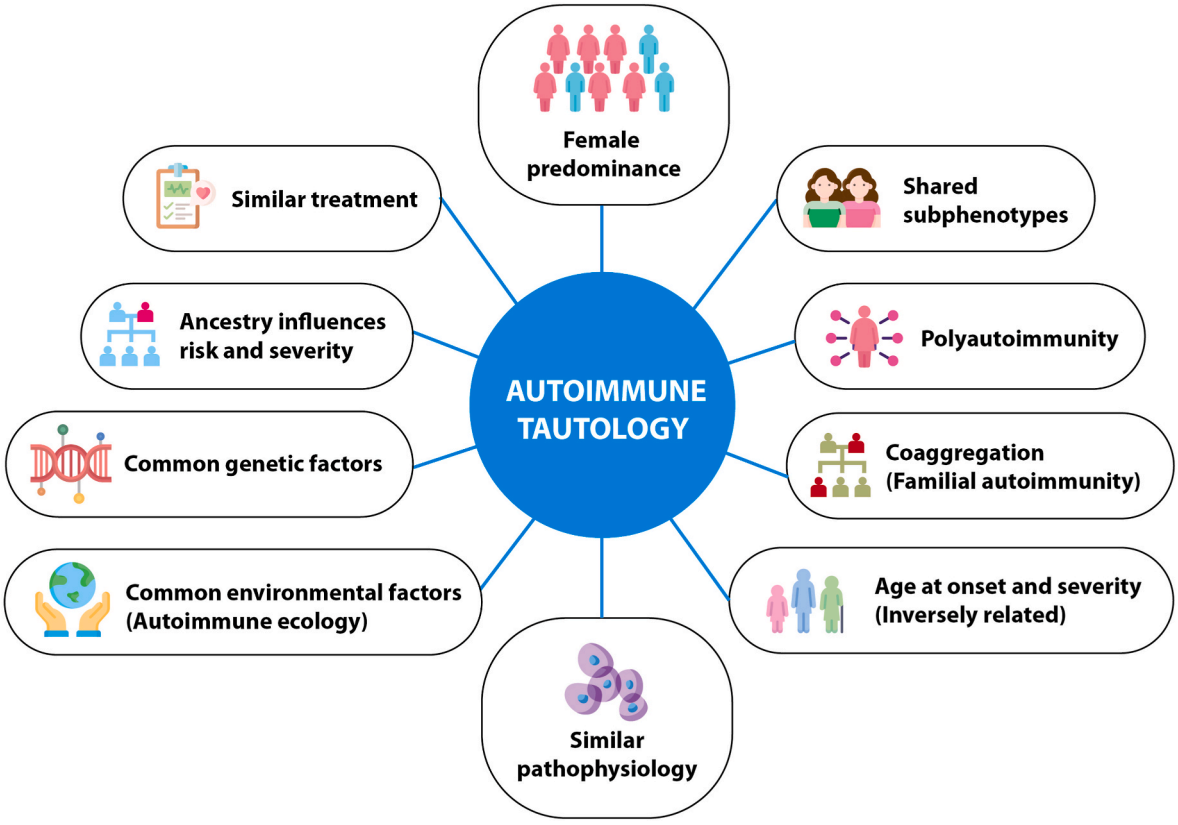

Fig. 1. Shared features of autoimmune diseases.

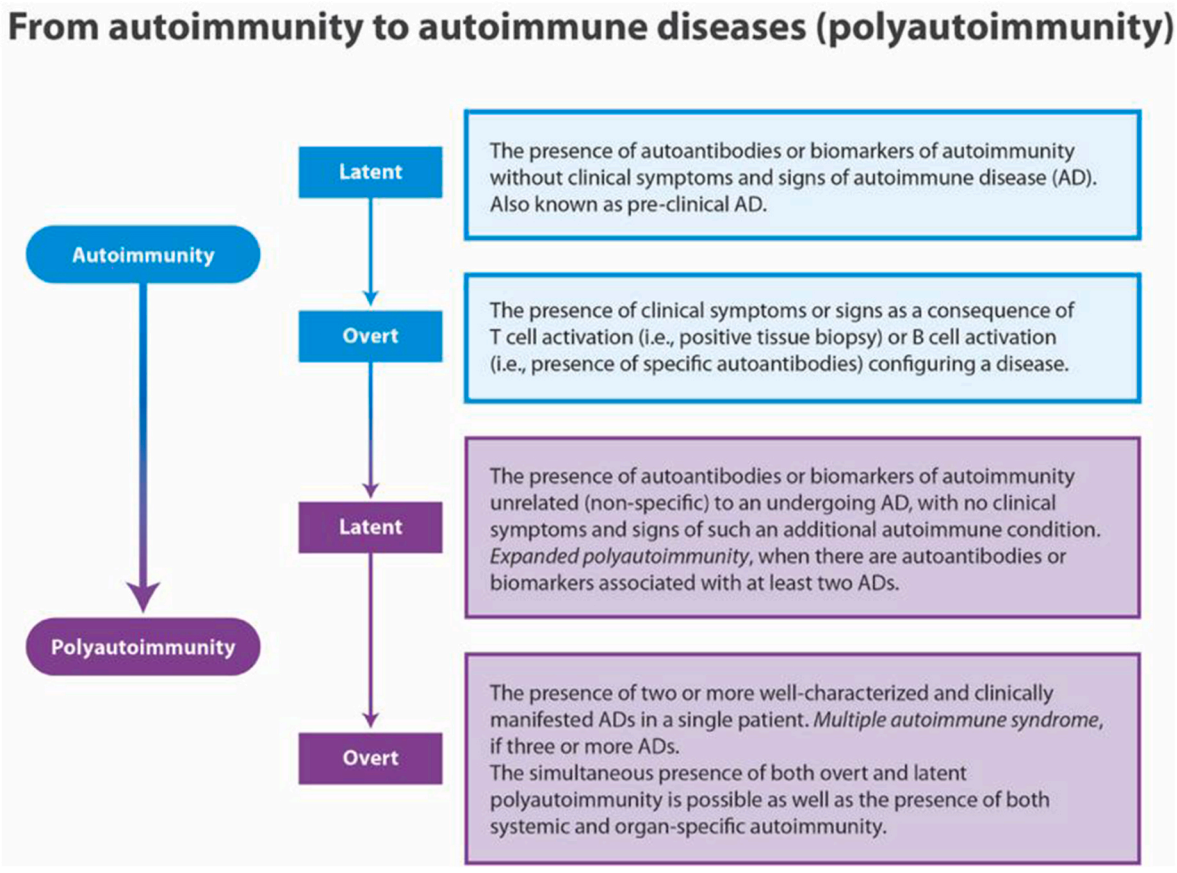

Fig. 2. From Autoimmunity to autoimmune diseases [42].

overt polyautoimmunity [15]. The significance of PolyA lies in the possibility of a new classification of autoimmune illnesses based on it [15].

In a systematic review and meta-analysis [16], of the prevalence of latent and overt PolyA on AITD, Graves' disease (GD) was the most prevalent autoimmune thyroid pathology. Overt PolyA was found in 13.46% of patients with AITD and latent PolyA in 17.45%. Within the PolyA types, type 1 diabetes (T1D) and autoimmune gastritis were the most representative, indicating that both latent and overt PolyA are common in AITD [16]. The study by Santos-Moreno et al. [17] found that 34.8% of their patients with SLE had PolyA, with antiphospholipid syndrome (APS) being the most frequent coexistent disease. PolyA in these patients was associated with sicca symptoms, thromboembolic phenomena, and fewer renal complications [17]. Unfortunately, this study did not evaluate the presence of AITD.

PolyA is a condition that may occur throughout the lifetime of an AD patient, as shown by the research of Bao et al. [18] in T1D. Even though PolyA has been identified in almost all ADs, the cross-sectional design of the majority of the studies is a factor explaining the varied PolyA prevalence rates among them.

One of the animal models of PolyA is the Non-Obese Diabetic (NOD) mice with autoimmune diabetes, in which PolyA is observed in relation with AITD and SS [19]. This phenomenon is promoted by targeting *AIRE* gen, IL-2 or performing thymectomy [19].

5. Familial autoimmunity

There are two types of familial clustering of ADs. The first and more common is coaggregation (i.e., familial autoimmunity), defined as the presence of diverse ADs in multiple members of a nuclear family. Second, familial autoimmune disease, where the same AD is observed in the nuclear family (i.e., aggregation) [20].

A Taiwanese study indicated that the risks of RA and other ADs increased in individuals with an RA family history, and approximately two-thirds of RA phenotypic variation was explained by familial factors [21]. Similarly, a Swedish study [22], reported that significant familial risks for discordant rheumatoid autoimmune diseases (i.e., familial autoimmunity) was observed for several ADs among patients with Polymyositis/Dermatomyositis (PM/DM), RA, SS, SLE and SSc. Another study estimated the heritability and genetic overlap in seven organ-specific ADs using a cohort of 11,814 twins [23]. Coaggregation was more pronounced in monozygotic twins (median hazard ratios (HR): 3.2, range: 2.2–9.2) than in dizygotic twins (median HR: 2.4, range: 1.1–10.0) [23]. Avalos-Díaz et al. [6], studied a set of monozygotic male twin patients who develop AITD and vitiligo associated with the HLA-DRB1*04-DQB1*03:02 and HLA-DRB1*03-DQB1*0201 haplotypes, exhibiting clinical data of multiple autoimmunity in relation to different epitopes that may be handled by MHC II molecules.

PolyA and familial autoimmunity represent extreme phenotypes that are ideal for identifying major genomic variants contributing to autoimmunity [2].

6. Age of onset

The age at onset of disease impacts the prognosis of ADs which tend to be more serious at a younger age of presentation. For instance, late-onset SLE (age at onset >50 years) is associated with less renal and neurological manifestations as compared to early-onset SLE (age at onset <50 years) [24]. Nevertheless, multimorbidity, where the co-occurrence of two conditions co-existing without any implicit ordering, can be a severity bias [25]. For this reason, the comparative analysis of ADs with respect to their prognosis based on age of onset, should be taken with caution, since older patients will have a greater burden of the same disease associated with other pathologies that may exacerbate or aggravate the underlying condition [26].

In autoimmune neurological diseases age at onset does not always influence the prognosis. A Spanish study classified myasthenia gravis (MG) based on early-onset (age at onset <50 years), late-onset (onset ≥50 and < 65 years), and very-late-onset MG (onset ≥65 years) and observed that patients with very-late-onset group presented with more life-threatening events. Late-onset MG and very-late-onset MG groups had more frequently ocular MG and a maximal worsening [27]. Neurological plasticity, especially in MS, reduce the effect of age at onset on severity. Cognitive impairment may be more accentuated in adults as compared to children, and not necessarily related. Butler Pagnotti et al. [28], compared cognition disease characteristics between adult onset (between the ages 20 and 40 years) versus late onset MS (onset after the age of 50 years), and showed that individuals with late onset disease had more impairment on tasks of visual learning and memory and working memory than the other group.

7. Similar pathophysiology

Loss of tolerance of the immune system and increased reactivity of T and B lymphocytes that end up causing tissue damage are characteristics of ADs. These disorders' similar heritability and genetic overlap point to a shared pathogenesis. In tissue damaged by autoimmunity, the predominant infiltrating cells include macrophages, neutrophils, autoreactive $CD8^+$ cytolytic T cells, and autoreactive $CD4^+$ T cells [2]. Increased number of memory $CD4^+$ T cells that promote autoimmunity has been observed in animal models of autoimmunity [29,30]. Among effector T cells, Th1, Th17, and Th9 cells contribute to the pathogenesis of ADs [31]. Defective regulatory function in T and B cells and activation of the type I interferon system are other important common mechanisms in ADs [2,32].

Kourilovitch et al. [4], studied neutrophil-to-lymphocyte ratio (NLR) as a biomarker who reflex complex processes orchestrated by neutrophils. An interval of 1–2 is considered as a normal value, 2–3 as a grey area indicating subclinical inflammation and values above 3 as inflammation. Authors indicated that NLR could be also interpreted as a predictor of relapses [4]. Duarte-Delgado et al. [10], report in this issue of the *Journal* similar metabolites and metabolic pathways associated with RA and SLE. In both diseases, there is a decrease in several amino acids and oxidative stress-related metabolites like glutathione [10].

In the NOD mouse models, as in people with AITD, the thyroid immune cell infiltration is predominantly composed of $CD4^+$, $CD8^+$, T cells, B cells and macrophages, demonstrating the similar pathophysiology with humans [19].

Tolerance defects are also an important mechanism leading to ADs. Alterations that lead to ineffective clearance of immune complexes and accumulation of apoptotic cells expose the immune system to various autoantigens; inappropriate cell death or survival is also believed to be involved in the pathogenesis of various ADs [33]. Autoantibodies appear before clinical symptoms, for example, ANA can appear 2.7–3.0 years before the diagnosis of SLE [2,34]. The risk of acquiring an AD (i.e., overt autoimmunity) rises in direct proportion to the quantity of autoantibodies present before the clinical symptoms occur [35].

8. Autoimmune ecology

Ecology (Greek: οἶκος, "house"; -λογία, "study of") studies the interactions between organisms and their environment [2,36]. Autoimmune ecology refers to the effect and relation between environmental factors and the risk and course of ADs [2,36]. Among them, tobacco, vitamin D, silicone, air pollution, and infectious agents have been the most studied.

Different infectious agents can trigger ADs, and a single one can affect the development of multiple ADs. *Campylobacter jejuni* and Zika virus have been cleared linked to the development of Guillain-Barré syndrome (GBS) [37,38]. *Yersinia enterocolitica* infection is associated with Hashimoto's thyroiditis (HT) [37]. Garcia-Carrasco's group [8], reviewed *H. pylori* infection and its association with ADs, like SLE, RA,

and SS. The role of *H. pylori* infection in this process remains unclear, but eradication should be recommended in patients with ADs or when a high risk of developing them exists. Posso-Osorio et al. [9], reviewed the human endogenous retroviruses (HERV) and non-HERV viruses incorporated into the human genome, supporting they are part of many research processes to understand their biological role in normal cell physiology and pathological processes such as ADs.

Vitamin D deficiency is a risk factor for developing ADs due to its impact on the microbiota, in addition to the immunomodulatory role through its receptor in dendritic cells, monocytes and T cells activation, mainly in inflammatory bowel disease (IBD), coeliac disease (CD), autoimmune hepatitis, T1D and AITD [39,40]. Vitamin D supplementation (2000 IU/day) for five years, with or without omega 3 fatty acids, reduced ADs by 22% [41].

Another recent aspect of autoimmune ecology is Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and Coronavirus disease (COVID-19) vaccines. SARS-CoV-2 is a new incriminating pathogen in the etiology of autoimmunity. There is a close relationship between SARS-CoV-2 infection and autoimmunity, first suggested by the presence of multiple autoantibodies that were associated with acute disease severity and mortality [42]. Patients with post-Covid syndrome present, several months after the acute illness, persistent inflammation and autoantibodies remain positive [43]. In addition, some patients develop overt ADs [44]. All of the above observations anticipated that "it would be possible to observe an increase incidence of ADs in the coming years and that, therefore, health and social care services will require a new framework to treat such patients" [45]. The large propensity score-matched cohort study by Chang et al. [46] confirmed the association between of COVID-19 and ADs.

Autoimmunity has been also described after vaccination against COVID-19. Rodríguez et al. [47], carried out an updated bibliographic review, where the most frequent diseases were immune thrombocytopenia, myocarditis and GBS, being widely prevalent among women.

Sasmaca et al. [3], review in this issue of the *Journal* the impact of the COVID-19 pandemic on patients with CD, finding an increased incidence during the COVID-19 pandemic. Multiple environmental factors may contribute to ADs, thus these interactions warrant further studies. For example, adherence to the diet is crucial for the patient's health and quality of life. Celiac disease is not uncommon among patients with ADs, therefore gluten-free diet have been advocated as a therapeutic tool in these patients [48].

Both latent and overt autoimmunity are dramatically increasing in many parts of the world, likely due to variations in exposures to environmental factors [49]. Therefore, more study on the autoimmune ecology is required. The understanding of how environmental variables affect gene activity is far more difficult to grasp, despite the fact that a sizable number of genetic variants associated with ADs have been uncovered.

9. Common genetic factors

The genetic influence on polygenic ADs are of two types: those which are common to several ADs (e.g., *PTPN22, HLADRB1*) and those that are specific to a certain condition (*INS* in T1D) [50]. There is a significant genetic overlap amongst ADs, as shown by the occurrence of pleiotropic variations that are common to several diseases and occasionally have opposite effects. The understanding of the genetics of ADs has much advanced in recent years [51–57], including the discovery of monogenic ADs as part of inborn errors of immunity [58,59].

Recent and elegant original works and reviews have pointed out the genetic commonalities among ADs [51,52,54,60–64], which include hundreds of loci, of which the major histocompatibility complex (MHC) region harbors the strongest susceptibility genes for ADs.

It is anticipated that new research examining how genetic variations affect gene expression (e.g., expression QTLs, splicing, methylation, and chromatin phenotypes) in particular tissues and cell types, will clarify the biological effects of genetic variations on disease [65]. It is also expected that additional approaches such as single cell analyses, 3D chromatin structure analysis or genome editing will allow to increase the knowledge of the genetic influence of genes on ADs. As a corollary, understanding the basic processes underlying genetic variations will offer the potential to enhance disease prevention and treatment options.

10. Ancestry

Ancestry refers to the common origin of a specific population, other terms like continental ancestry and genetic ancestry, are described [66]. In ADs, genetic ancestry strongly contributes to the clinical heterogeneity, variation, and treatment response [2]. For example, African-Americans (AA) have shown 3 to 5 times more risk to develop SLE, compared with individuals with European ancestry (EA) [67]. Lupus nephritis is more severe on AA and Hispanic population, than in Europeans [67]. Ancestry influences the susceptibility of several others ADs including SS [66] T1D [68], RA [53], among others.

Ancestral differences in immune cells may contribute to the different disease course and incidence between populations [69]. Ancestry influences gene expression signatures. Much of the gene expression in patients with SLE is related to patient ancestry resulting in alterations in the proportions of hematopoietic cells, cellular processes, and signaling pathways detected [70]. There is a significant association between autoantibody profiles and differences in gene expression between ancestries (i.e., AA vs EA vs Native American ancestry) [70].

Guavita-Navarro et al. [7], compare the sensitivity of the European league against rheumatism/American College of rheumatology (EULAR/ACR) 2019 and Systemic Lupus International Collaborating Clinics (SLICC) 2012 classification criteria in a group of SLE patients of Latin American population of Amerindian ancestry. They observed no differences between the EULAR/ACR and SLICC 2012 criteria in the population studied.

To date, studies of the genetics of ADs, including ancestry, have largely focused on EA populations. In the near future, ancestry will be the understanding basis of several clinical and treatment variations between individuals with the same AD.

11. Similar treatment

The final premise of the autoimmune tautology theory follows from the earlier ones and corresponds to the fact that ADs receive identical therapies. Conventional synthetic disease-modifying antirheumatic drugs are widely used for ADs, being the first line of treatment in many ADs [71].

There are biological and synthesis inhibitors therapies such as Janus kinase (JAK) inhibitors (e.g., Tofacitinib). Within biological therapies, B cell depletion, by direct depletion with monoclonal antibodies (e.g., rituximab) and indirect depletion via survival cytokine blockade (e.g., belimumab) [72] are used for several ADs. JAK inhibitors are currently used to treat RA, psoriatic arthritis, alopecia areata, vitiligo, discoid lupus erythematosus, dermatomyositis, SLE, SS and IBD [73,74]. Finally, drug repurposing based on the physiopathology of ADs will also improve the treatment of ADs [75].

12. Conclusion

The heterogeneity of ADs may be attributable to a collection of diverse disorders based on epidemiology, pathology, or diagnostic findings, but the underlying physiopathological mechanisms are common. Identification of such common mechanisms will improve our comprehension of these complex, common, and sometimes devastating diseases and allow us to develop a new taxonomy, predict their occurrence, and discover new therapeutic interventions.

Note added in proof. A recent work by Nathalie Conrad and colleagues showed that the prevalence of ADs in the UK was 10·2%, and

that the number of new AD diagnoses increased by 22% during their study period (2017–19 vs 2000–02 IRR 1·22 [1·18–1·28]), largely due to polyautoimmunity [76].

Credit author statement

Juan-Manuel Anaya: Conceptualization, writing and editing. Santiago Beltrán: writing and editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Juan-Manuel Anaya*, Santiago Beltrán
Health Research and Innovation Center at Coosalud, Cartagena, 130001, Colombia

* Corresponding author.
E-mail address: janaya@coosalud.com (J.-M. Anaya).